Release Rates of Solid Drug Mixtures Dispersed in Inert Matrixes III: Binary Mixture of Acid Drugs Released into Alkaline Media

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Abstract □ The release of a mixture of two acidic drugs (benzoic acid and salicylic acid) from an inert matrix into phosphate buffers was investigated utilizing the physical model approach. Equations were derived describing the diffusional behavior and interactions of the various species under different conditions. The equations were solved for two boundary conditions due to the interactions of drugs with the buffers and drugs by themselves, *i.e.*, for precipitation or no precipitation of benzoic acid in the matrix. Experimental data were obtained and analyzed with self-consistent methods employing the appropriate equations. The analysis showed that the physical model investigated generally described all of the experimental data and yielded physically significant parameter values and conclusions. It was found that the model utilizing the simultaneous precipitation and drug release gave much better agreement of the data with the theory than that which assumed appreciable supersaturation of the drug in the matrix.

Keyphrases □ Release rates of solid drug mixture (benzoic–salicylic acids) embedded in inert matrix—effect of alkaline solvent, equations □ Benzoic acid–salicylic acid mixture—release from inert matrix, effect of alkaline phosphate solvent, equations □ Drug mixtures, solid (benzoic–salicylic acids)—release rates from inert matrixes, effect of alkaline solvent, equations □ Binary drug systems—release from inert matrix, effect of alkaline phosphate solvent, equations

Previous publications (1–9) discussed the results of investigations designed to quantitate the influence of numerous factors upon the release profile of drugs embedded in an inert matrix into solvent media. The initial studies (1–4, 8–11) quantitated the role of the media, the inert matrix, and drug characteristics on the release profile of a single drug. More recently, this work was extended to binary drug systems (5, 6, 12). In particular, the release rates of the binary system, benzoic acid and salicylic acid, were studied utilizing 0.1 *N* HCl as the solvent system. The use of 0.1 *N* HCl greatly simplified the release pattern since both acids are undissociated at this pH. The less complex study demonstrated the validity of the binary drug release model and allowed the parameters of the system to be accurately determined. This necessary baseline study also essentially described the release profile of any two weak acids into an acidic medium with a pH similar to that of gastric fluid, which is essentially a nonreactive medium for this drug system.

The purposes of this study were to investigate the influence of a more alkaline medium representative of the intestinal lumen, to develop a model applicable to this system, and to test the model experimentally. Obviously, an alkaline medium will complicate the model considerably, since the acids will be converted to their dissociated form when dissolved by the alkaline medium. The degree of conversion to the dissociated form will depend, of course, not only on the pH but also on the buffer capacity of the medium relative to the amounts of acids embedded in the matrix. This system is further complicated by possible mutual interaction of the two acids when the pH and buffer capacity of the medium are not sufficient to convert totally both acids to their respective dissociated forms. For this reason, the release profile of this binary system was determined at various phosphate buffer concentrations for the pH range of 5–8.

The results of this study complement the previous work determined in acidic media and should provide a better understanding of the effect of the biological parameters on the release of these drugs when administered orally. In addition, the results of these studies permit the evaluation of the often-made assumption that the release medium is not important due to the relatively long diffusional pathway within the inert matrix as compared to the outer diffusion layer. From a biopharmaceutical viewpoint, this is obviously an important consideration when attempting to control the release rate as the tablet passes through the GI tract. It is hoped that the results of this investigation will lead to a better understanding of the expected release patterns of these systems in the tract and, therefore, to their wider acceptance, since it is generally acknowledged that more definite control of the release pattern of drug after administration must be achieved if we are to improve future health care significantly. It is believed that timed-release medication is one area that must be thoroughly investigated, since it potentially provides numerous easily controlled variables necessary for success in obtaining a desirable release profile of a drug.

THEORY

The relative release rate of a mixture of two drugs dispersed in an inert matrix has been shown to depend on their relative solubilities, relative diffusion coefficients, and relative amounts incorporated in the matrix (5). Therefore, the interface existing between the solid drug and solvent for the two drugs recedes at different rates. The one-dimensional diffusion-controlled model proposed for the release of a mixture of benzoic acid and salicylic acid, which is dispersed in a matrix into a phosphate-buffered solution, is shown in Fig. 1 for the case in which the solid benzoic acid solvent interface, s_1, moves more slowly than the solid salicylic acid-solvent interface, s_2.

Figure 1*a* illustrates the system when the inert matrix is first exposed to solvent. At this time, no solvent penetration has occurred and, therefore, both solid drug solvent interfaces have not as yet receded into the inert matrix. Figure 1*b* shows the conditions existing at a finite time later, t. The model essentially shows four regions. The boundary of the inert matrix surface solvent interface is at $x = 0$, and separates Region 0 (bulk solvent) and Region 1 (completely leached portion of the matrix). The solid–liquid boundary of the slower moving drug (benzoic acid) is at $x = s_1$ and separates Region 1 and Region 2, which contains a solid phase

composed of benzoic acid only. Finally, the solid–liquid boundary of the faster moving drug (salicylic acid) is at $x = s_2$ and separates Region 2 from Region 3, which contains both drugs as solids. Any solvent that exists in Region 3 will be saturated with respect to both benzoic acid and salicylic acid. Similarly, for the boundary s_2, the solution will be saturated with respect to both salicylic acid and benzoic acid. In Region 2, the situation is changed, since the solution will be saturated with respect to only benzoic acid. The salicylic acid, on the other hand, will show a concentration gradient in this region. Conversely, none of the concentrations in Region 1 remains constant; therefore, a concentration gradient exists for all species in this region. Since the solvent will be considered an infinite sink, Region 0 will essentially contain only phosphate buffers.

From this model, differential equations were obtained which describe the diffusional behavior of the various species in Regions 1 and 2. For the equations to be developed in this section, D is the diffusion coefficient of the species in the solvent and is assumed for the sake of simplicity to be the same for all species involved in Eqs. 1-8. The porosities (5) in Regions 1 and 2 are designated as ϵ_1 and ϵ_2. The tortuosities (5) in the same regions are designated as τ_1 and τ_2, respectively. The model takes into consideration the fact that as the phosphate buffer solvent penetrates the matrix, it will interact with both the benzoic acid and salicylic acid to form benzoate and salicylate ions, respectively. The model, therefore, must consider the concentration gradients of all species in Regions 1 and 2.

Since the rate of transport of dibasic phosphate ion, HP^{-2}, into the matrix must be equal to the rate of transport of monobasic phosphate ion, H_2P^-, out of the matrix, it follows that:

$$D\frac{\epsilon_1}{\tau_1}\frac{d(HP^{-2})}{dx} + D\frac{\epsilon_1}{\tau_1}\frac{d(H_2P^-)}{dx} = 0 \qquad \text{(Eq. 1)}$$

In addition, the transport rate of H_2P^- must be equal to the sum of the diffusion rates of salicylate ion, S^-, and benzoate ion, B^-; therefore, the following must be true:

$$D\frac{\epsilon_1}{\tau_1}\frac{d(B^-)}{dx} + D\frac{\epsilon_1}{\tau_1}\frac{d(S^-)}{dx} = D\frac{\epsilon_1}{\tau_1}\frac{d(H_2P^-)}{dx} \qquad \text{(Eq. 2)}$$

The total transport rates, G_S and G_B, out of the matrix for salicylic and benzoic acids, HS and HB, respectively, are given by the following equations:

$$D\frac{\epsilon_1}{\tau_1}\frac{d(HS)}{dx} + D\frac{\epsilon_1}{\tau_1}\frac{d(S^-)}{dx} = G_S \qquad \text{(Eq. 3)}$$

$$D\frac{\epsilon_1}{\tau_1}\frac{d(HB)}{dx} + D\frac{\epsilon_1}{\tau_1}\frac{d(B^-)}{dx} = G_B \qquad \text{(Eq. 4)}$$

In the same manner, four similar equations can be obtained for Region 2:

$$D\frac{\epsilon_2}{\tau_2}\frac{d(HP^{-2})}{dx} + D\frac{\epsilon_2}{\tau_2}\frac{d(H_2P^-)}{dx} = 0 \qquad \text{(Eq. 5)}$$

$$D\frac{\epsilon_2}{\tau_2}\frac{d(B^-)}{dx} + D\frac{\epsilon_2}{\tau_2}\frac{d(S^-)}{dx} = D\frac{\epsilon_2}{\tau_2}\frac{d(H_2P^-)}{dx} \qquad \text{(Eq. 6)}$$

$$D\frac{\epsilon_2}{\tau_2}\frac{d(HS)}{dx} + D\frac{\epsilon_2}{\tau_2}\frac{d(S^-)}{dx} = G_S' = G_S \qquad \text{(Eq. 7)}$$

$$D\frac{\epsilon_2}{\tau_2}\frac{d(B^-)}{dx} + D\frac{\epsilon_2}{\tau_2}\frac{d(HB)}{dx} = G_B' \qquad \text{(Eq. 8)}$$

where G_S' and G_B' are the total transport rates of salicylic and benzoic acids out of Region 2, respectively. The rate of total transport of salicylic acid species out of the matrix, G_S, is equal to the rate of transport out of Region 2, G_S', since Region 2 is rate controlling. G_B', however, is not equal to G_B since Region 1 is rate controlling.

By assuming that the concentration of all drugs is zero in the bulk solution at all times, that is, the solvent acts as a perfect sink, Eqs. 1-4 can be integrated from $x = 0$ to $x = s_1$ to give:

$$(HP^{-2})_1 + (H_2P^-)_1 = TP \qquad \text{(Eq. 9)}$$

$$(B^-)_1 + (S^-)_1 = (H_2P^-)_1 - (H_2P^-)_0 \qquad \text{(Eq. 10)}$$

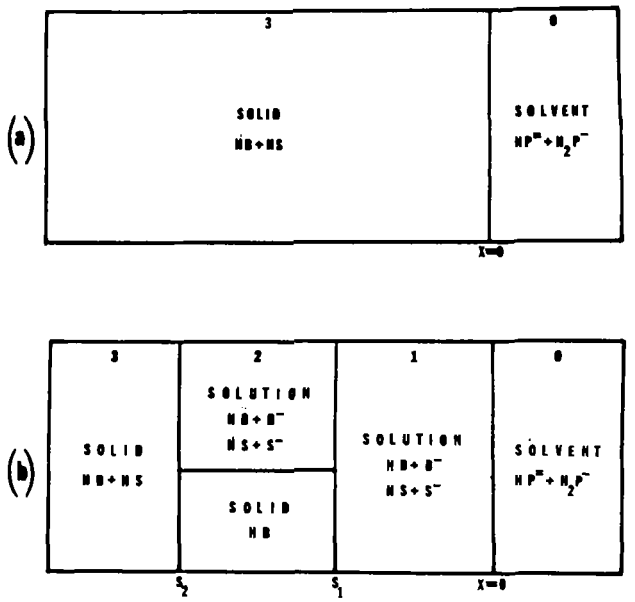


Figure 1—*Diffusion-controlled model for the release of a mixture of benzoic acid, HB, and salicylic acid, HS, embedded in an inert matrix into a phosphate buffer solution for the case in which the benzoic acid boundary,* s_1, *moves more slowly than the salicylic acid boundary,* s_2. *Key: (a), conditions existing at* t = 0; *and (b), conditions at a finite time,* t *later. Salicylate and benzoate ions are represented by* S^- *and* B^-, *respectively.*

$$(HS)_1 + (S^-)_1 = \frac{G_S s_1}{D\frac{\epsilon_1}{\tau_1}} \qquad \text{(Eq. 11)}$$

$$(HB)_1 + (B^-)_1 = \frac{G_B s_1}{D\frac{\epsilon_1}{\tau_1}} \qquad \text{(Eq. 12)}$$

Equations 4-8 can also be integrated from $x = s_1$ to $x = s_2$ to yield Eqs. 13-16:

$$(HP^{-2})_2 - (HP^{-2})_1 + (H_2P^-)_2 - (H_2P^-)_1 = 0 \qquad \text{(Eq. 13)}$$

$$(B^-)_2 - (B^-)_1 + (S^-)_2 - (S^-)_1 = (H_2P^-)_2 - (H_2P^-)_1 \qquad \text{(Eq. 14)}$$

$$(HS)_2 - (HS)_1 + (S^-)_2 - (S^-)_1 = \frac{G_S(s_2 - s_1)}{D\frac{\epsilon_2}{\tau_2}} \qquad \text{(Eq. 15)}$$

$$(B^-)_2 - (B^-)_1 + (HB)_2 - (HB)_1 = \frac{G_B'(s_2 - s_1)}{D\frac{\epsilon_2}{\tau_2}} \qquad \text{(Eq. 16)}$$

The subscripts 0, 1, and 2 denote the concentration of the respective species at $x = 0$, $x = s_1$, and $x = s_2$. The TP is the total concentration of all species of the phosphate buffer.

It was also assumed that the following equilibria exist in all regions: $HS + HP^{-2} \leftrightarrows S^- + H_2P^-$ and $HB + HP^{-2} \leftrightarrows B^- + H_2P^-$, and obey the following relationships:

$$K_1 = \frac{(S^-)(H_2P^-)}{(HS)(HP^{-2})} = \frac{K_{HS}}{K_{2P}} \qquad \text{(Eq. 17)}$$

$$K_2 = \frac{(B^-)(H_2P^-)}{(HB)(HP^{-2})} = \frac{K_{HB}}{K_{2P}} \qquad \text{(Eq. 18)}$$

where K_{HS} and K_{HB} are the acid dissociation constants of salicylic acid and benzoic acid, respectively, and K_{2P} is the second acid dissociation constant of phosphoric acid. The conditions are such that the principal equilibrium governing the system obtained from the above equilibria is given by: $HS + B^- \leftrightarrows HB + S^-$.

The above equilibrium indicates that the benzoate ion will be converted to benzoic acid in Region 2, since K_{HB} is smaller than K_{HS}. In addition, the presence of solid HB in Region 2 dictates

that the benzoic acid concentration in Region 2 as a minimum must be equal to its intrinsic solubility. Since the benzoate ion is being converted to benzoic acid in Region 2, there are two physically reasonable or possible cases in this region: either precipitation of HB somewhere in Region 2 will occur or Region 2 will become supersaturated with respect to HB. These two possibilities are considered separately in the following two sections.

Case I (Precipitation in Region 2 Allowed)—A suitable set of boundary conditions can be specified for the case in which precipitation of HB in Region 2 is permitted. By assuming that the rate of precipitation in Region 2 is sufficiently rapid, it can be assumed that the concentration of HB in solution is equal to its intrinsic solubility. Therefore, the boundary conditions for HB in Region 2 are equal for this case, *i.e.*, $(HB)_2 = (HB)^* = (HB)_1$. The absence of solid HS in Region 2, however, means that the concentration of HS in Region 2 will be less than its intrinsic solubility. Therefore, a saturated solution of HS will exist only at the boundary, s_2, *i.e.*, $(HS)_2 = (HS)^* > (HS)_1$, where $(HS)^*$ is the intrinsic solubility for salicylic acid. It should be emphasized that these boundary conditions are consistent with the assumption that the processes are all diffusion controlled and that rapid equilibria among species and phases exist at any coordinate, x. Because of this precipitation, the net transport rate of total benzoate and benzoic acid in Region 2, G_B', may not be zero.

By simultaneously solving Eqs. 9–18, equations were obtained which can be used to describe the drug release as a function of time. To test the model, these equations were solved to obtain expressions which can be used to analyze experimental data. The following expression involving the rate of total salicylic acid (all species) was obtained by analysis of Region 2 equations:

$$G_{Bs_2} = D\frac{\epsilon_2}{\tau_2}\left\{(HS)^* + \frac{K_{HS}(HS)^*}{K_{2P}(H_2P^-)_2}[(TP) - (H_2P^-)_2] + \frac{G_{Bs_1}}{D}\left[\frac{\tau_2}{\epsilon_2} - \frac{\tau_1}{\epsilon_1}\right]\right\} \quad \text{(Eq. 19)}$$

In addition, an expression involving the rate of total salicylic acid obtained by analysis of Region 1 equations was found to be given by:

$$G_{Bs_1} = D\frac{\epsilon_1}{\tau_1}\left\{(HS)_1 + \frac{K_{HS}(HS)_1}{K_{2P}(H_2P^-)_1}[(TP) - (H_2P^-)_1]\right\} \quad \text{(Eq. 20)}$$

For convenience of analysis, as will later be seen, the expression was not solved explicitly for G_B.

In these expressions, the quantities $(HS)_1$, $(H_2P^-)_1$, and $(H_2P^-)_2$ cannot be experimentally measured and the following expressions containing measurable quantities can be substituted for them:

$$(HS)_1 = [(H_2P^-)_1 - (H_2P^-)_0]\frac{K_{2P}(H_2P^-)_1}{K_{HS}[(TP) - (H_2P^-)_1]} - \frac{K_{HB}(HB)^*}{K_{HS}} \quad \text{(Eq. 21)}$$

$$(H_2P^-)_1 = \frac{A}{\left(G_{Bs_1}/D\frac{\epsilon_1}{\tau_1}\right) + B} \quad \text{(Eq. 22)}$$

$$(H_2P^-)_2 = \frac{F + \sqrt{F^2 + \frac{4E(TP)}{K_{2P}}}}{2} \quad \text{(Eq. 23)}$$

where:

$$A = \frac{K_{HB}}{K_{2P}}(HB)^*(TP)$$

$$B = \frac{(HB)^*}{K_{2P}}[K_{HB} - K_{2P}]$$

$$F = (H_2P^-)_1 - C - \frac{E}{K_{2P}}$$

$$C = \frac{[(TP) - (H_2P^-)_1]}{K_{2P}(H_2P^-)_1}[K_{HS}(HS)_1 + K_{HB}(HB)^*]$$

$$E = K_{HS}(HS)^* + K_{HB}(HB)^*$$

It is seen that if Eqs. 21–23 are substituted into Eqs. 19 and 20, the rates of salicylic acid release from Regions 1 and 2 can be calculated from experimentally available measurements for the precipitation model.

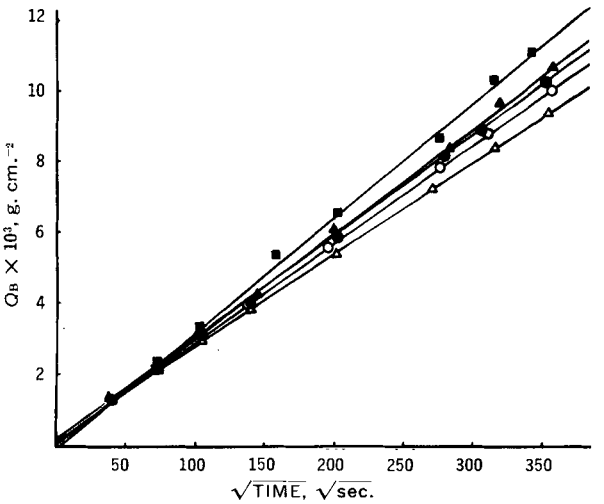


Figure 2—*Release of benzoic acid from an inert matrix [polyethylene–polyvinyl chloride (3:7)] containing 20% of a mixture of 3:1 ratio of benzoic to salicylic acid into phosphate buffer (KH_2PO_4–K_2HPO_4 = 9:1 molar ratio) at different total phosphate concentrations. Key: ■, 0.50 M; ▲, 0.25 M + 0.01% dioctyl sodium sulfosuccinate; △, 0.25 M; ●, 0.10 M + 0.01% dioctyl sodium sulfosuccinate; and ○, 0.10 M phosphate concentration.*

Case II (Supersaturation in Region 2)—Although it was recognized that this case is the less likely one due to the difficulty of maintaining a supersaturated solution of HB in the presence of its solid phase, it was felt that the possibilities were such that it should be fully investigated. In addition, this analysis may lead to a better understanding of this system and to more confidence in the results and conclusions. This case involves the following boundary conditions: $G_B' = 0$, $(HB)_1 = (HB)^*$, and $(HS)_2 = (HS)^*$. In this case, $(HB)_2 \neq (HB)^*$, since its concentration is higher due to no precipitation occurring in Region 2. In addition, the total concentration of all benzoic acid species is constant in all parts of Region 2 for this case. Although the slope of the concentration profiles of both species, HB and B^-, are not zero in Region 2, the total concentration of both species remains constant as the slopes are equal in magnitude but opposite in sign in this region; therefore, no net movement of the HB species occurs in Region 2. For this case, the solution of Eqs. 9–18 yielded the same four equations, Eqs. 19–22, as in the precipitation model. However, the expression for $(H_2P^-)_2$ is changed and is given by Eq. 24:

$$\alpha(H_2P^-)_2^3 + \beta(H_2P^-)_2^2 + \gamma(H_2P^-)_2 + \Delta = 0 \quad \text{(Eq. 24)}$$

where:

$$\alpha = \frac{L}{TP}$$

$$\beta = \frac{K_{HS}(HS)^*L}{(TP)K_{2P}} + \frac{ML}{(H_2P^-)_1} - \frac{ML}{(TP)} - 1 - \frac{G_{Bs_1}}{D\frac{\epsilon_1}{\tau_1}(TP)} - \frac{(H_2P^-)_1L}{(TP)}$$

$$\gamma = \frac{G_{Bs_1}}{D\frac{\epsilon_1}{\tau_1}} - \frac{K_{HS}(HS)^*L}{K_{2P}} - \frac{K_{HS}(HS)^*}{K_{2P}} - \frac{M(TP)}{(H_2P^{-2})_1} + M + (H_2P^-)_1$$

$$\Delta = \frac{K_{HS}(HS)^*TP}{K_{2P}}$$

$$L = \frac{K_{HB} - K_{2P}}{K_{HB}}$$

$$M = \frac{K_{HB}(HB)^* + K_{HS}(HS)_1}{K_{2P}}$$

It is seen that if Eqs. 21, 22, and 24 are substituted into Eqs. 19 and 20, the rates of salicylic acid release from Regions 1 and 2

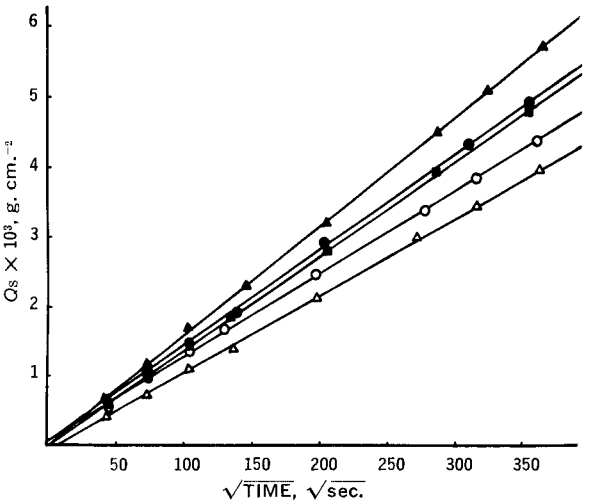


Figure 3—*Release of salicylic acid from an inert matrix [polyethylene–polyvinyl chloride (3:7)] containing 20% of a mixture of 3:1 ratio of benzoic to salicylic acid into phosphate buffer (KH_2PO_4–K_2HPO_4 = 9:1 molar ratio) at different total phosphate concentrations. Key: ■, 0.50 M; ▲, 0.25 M + 0.01% dioctyl sodium sulfosuccinate; △, 0.25 M; ●, 0.10 M + 0.1% dioctyl sodium sulfosuccinate; and ○, 0.10 M phosphate concentration.*

can be calculated from experimentally available measurements for the supersaturation model.

EXPERIMENTAL

Materials—Singh *et al.* (5) found that a mixture of polyvinyl chloride[1] and polyethylene[2] in a 7:3 w/w ratio forms a useful matrix for a number of drug mixtures. Therefore, in the present studies this mixture ratio was used for the matrix. Benzoic acid (reagent grade)[3] and salicylic acid (reagent grade)[3] were purified by recrystallization from an ethanol–water mixture and dried at 100°. The dried powders were mixed in a 1:3 w/w ratio of salicylic acid to benzoic acid and then added to a prepared 7:3 w/w mixture of polyvinyl chloride and polyethylene powders so that the final mixture contained 80% total plastic (polyvinyl chloride and polyethylene) by weight. The 1:3 ratio of the salicylic acid to benzoic acid was used to assure the situation in which solid benzoic acid rather than salicylic acid would exist in Region 2 for all pH conditions anticipated.

Tablet—A tablet was made by compressing 300 mg. of the drug–plastic mixture using a press[4] at a force of 4540 kg. (10,000 lb.) with a 1.27-cm. (0.5-in.) flat-face die and punch. It was then mounted in wax by coating the lateral and one of the flat sides with molten beeswax, thereby exposing only one flat surface of the tablet for drug release. The solid concentrations of the drug and the volume fractions of drugs and air in the tablets were determined as previously described (1). The parameters are needed for a theoretical treatment of data.

Release Rate—The apparatus used for these release rates was similar to that used by Singh *et al.* (7). In a typical experiment, after the introduction of solvent, aliquots of solution were removed as a function of time for both acids; their concentrations in the bulk were determined by UV spectrophotometric analysis at 296 and 259 nm. The solvents used in these studies contained phosphate buffers which consisted of different ratios of dipotassium phosphate[3] and monopotassium phosphate[3] to control the pH and of different total buffer concentrations in order to control the degree of interaction with the drugs. In addition, the effect of surfactant was investigated by adding dioctyl sodium sulfosuccinate[5] to the solvent of a number of studies.

[1] Dow Chemical Co., Midland, Mich.; particle size <80 mesh.
[2] Allied Chemical Corp., Plastic Division, Morristown, N. J.; particle size <270 mesh.
[3] J. T. Baker Chemical Co., Phillipsburg, N. J.
[4] Fred S. Carver, M. C., Summit, N. J.
[5] Aerosol OT, American Cyanamid Co., Wayne, N. J.

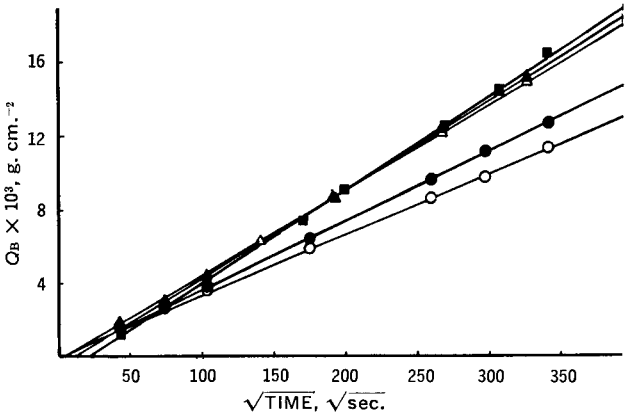


Figure 4—*Release of benzoic acid from an inert matrix [polyethylene–polyvinyl chloride (3:7)] containing 20% of a mixture of 3:1 ratio of benzoic to salicylic acid into phosphate buffer (KH_2PO_4–K_2HPO_4 = 1:1 molar ratio) at different total phosphate concentrations. Key: ■, 0.50 M; ▲, 0.25 M + 0.01% dioctyl sodium sulfosuccinate; △, 0.25 M; ●, 0.10 M + 0.01% dioctyl sodium sulfosuccinate; and ○, 0.10 M phosphate concentration.*

RESULTS

Some of the experimental results are presented in Figs. 2–5. The most noteworthy aspect of these results is that all of the experimental data appear to follow the square root of time dependence.

By comparing Figs. 2 and 4, it can be seen that with the same concentrations of solvent but a different pH, the solution of higher pH yields the faster rate for benzoic acid (almost two times faster). The same results are shown for salicylic acid in Figs. 3 and 5. Figures 4 and 5 show that the buffer with the same ratio of dipotassium phosphate and monopotassium phosphate yields the faster release rate when the concentration of buffer is higher. From these figures it can also be seen that solvents with dioctyl sodium sulfosuccinate yield faster release rates for the same concentration in the absence of dioctyl sodium sulfosuccinate. The presence of dioctyl sodium sulfosuccinate has been shown (7) to provide complete solvent penetration of the matrix. These results show that the release rate is a function of the buffer pH, buffer concentration, and the permeation rate of the solvent.

TREATMENT OF EXPERIMENTAL DATA AND COMPARISON OF RESULTS WITH THEORY

Because of the very complex nature of the equations, it would be extremely difficult to test the theory in the usual manner (5, 6),

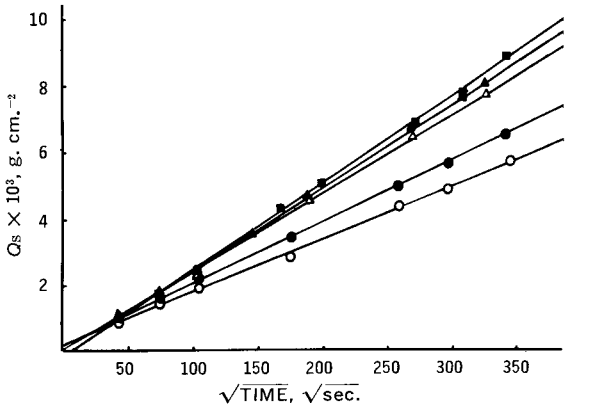
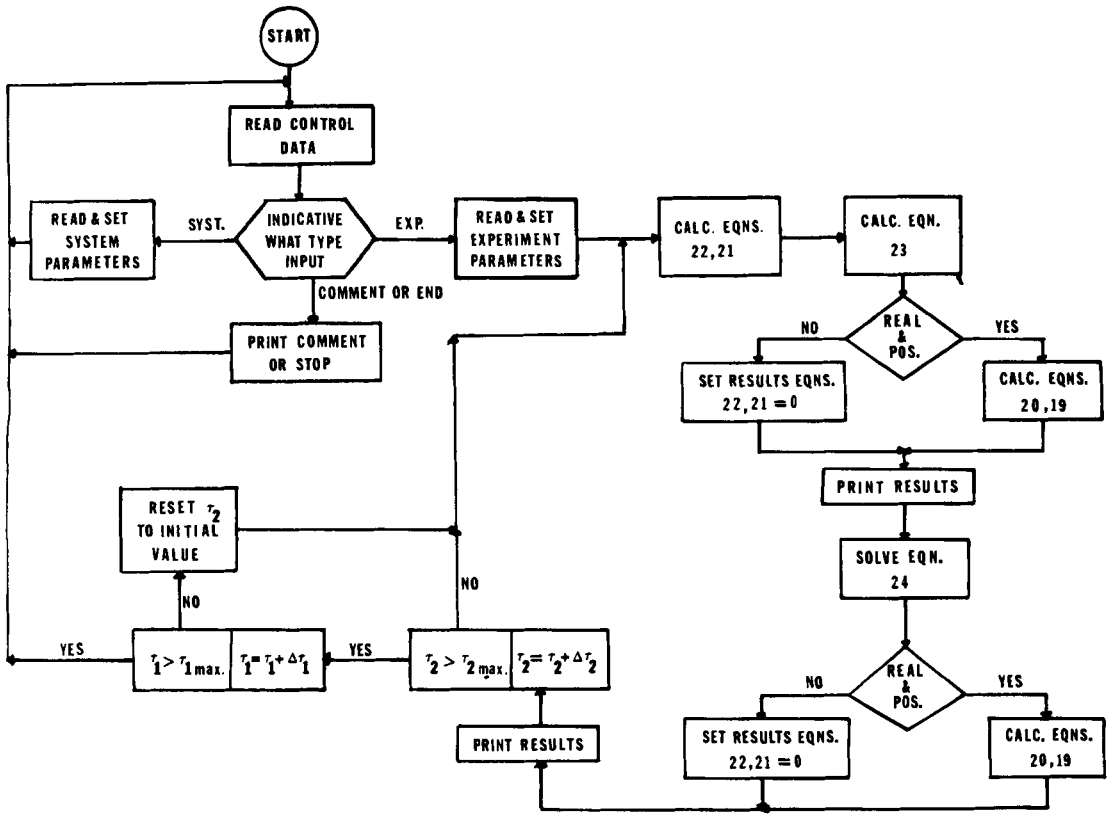


Figure 5—*Release of salicylic acid from an inert matrix [polyethylene–polyvinyl chloride (3:7)] containing 20% of a mixture of 3:1 ratio of benzoic to salicylic acid into phosphate buffer (KH_2PO_4–K_2HPO_4 = 1:1 molar ratio) at different total phosphate concentrations. Key: ■, 0.50 M; ▲, 0.25 M + 0.01% dioctyl sodium sulfosuccinate; △, 0.25 M; ●, 0.10 M + 0.01% dioctyl sodium sulfosuccinate; and ○, 0.10 M phosphate concentration.*



Scheme I—Flowchart for computer program showing the procedure used to estimate τ_1 and τ_2 for the release of benzoic and salicylic acids into phosphate buffer.

i.e., to compare directly experimental and theoretically calculated rates in the theoretical equations, parameters that have been determined either *a priori* or from experiments other than the release rate experiments themselves. It was found that the theoretical model was best investigated by using a self-consistency approach involving the use of the derived equations with experimental data.

The particular approach taken to compare the experimental results with theory may be described as follows. The experimental values for G_{BS_1} were used with Eqs. 19 and 20 to yield a function of τ_1 and τ_2. Then the τ_1 and τ_2 values were adjusted to obtain simultaneously the best agreement between the theoretical and experimental G_{SS_2} values and s_2/s_1 ratios. The success of this method depends heavily upon having a wide range of release rates which are necessary for a sensitive test of the theory.

As shown in the *Appendix*, it was found that:

$$G_{BS_1} = \frac{1}{2A_{HB}}\left(\frac{Q_B}{t^{1/2}}\right)^2 \qquad \text{(Eq. 25)}$$

$$G_{SS_2} = \frac{1}{2A_{HS}}\left(\frac{Q_S}{t^{1/2}}\right)^2 \qquad \text{(Eq. 26)}$$

$$\frac{s_2}{s_1} = \left(\frac{G_{SS_2} \cdot A_{HB}}{G_{BS_1} \cdot A_{HS}}\right)^{1/2} \qquad \text{(Eq. 27)}$$

where A_{HB} and A_{HS} are the concentrations of solid HB and solid HS incorporated in the matrix, respectively; and $Q_B/t^{1/2}$ and $Q_S/t^{1/2}$ are the slopes of plots of the experimental release of benzoic acid and salicylic acid against the square root of time, respectively. Equations 25–27 may then be used to calculate the experimental G_{BS_1}, G_{SS_2}, and s_2/s_1, respectively. The theoretical G_{SS_2} was obtained from Eq 19, and the theoretical s_2/s_1 was obtained from:

$$\frac{s_2}{s_1} = \frac{G_{SS_2} \text{ obtained from Eq. 19}}{G_{SS_1} \text{ obtained from Eq. 20}} \qquad \text{(Eq. 28)}$$

The calculations of τ_1 and τ_2 from Eqs. 19 and 20 were carried out using a digital computer[6]. The flowchart for the computer program is shown in Scheme I for both boundary conditions. The "system parameters" shown in the flowsheet are all of the parameters given by the equations presented in the theory section that are constant for a given system; these are K_{HB}, K_{HS}, (HB)*, (HS)*, D, ϵ_1, and ϵ_2.

On the other hand, the "experimental parameters" shown in the flowsheet are those that are different for each system studied depending on the experimental conditions utilized; these are (TP), $(H_2P^-)_0$, G_{BS_1}, τ_1, τ_2, $\Delta\tau_1$ (which is an increment of τ_1), and $\Delta\tau_2$ (which is an increment of τ_2).

Table I shows the computation of G_{SS_2} and s_2/s_1 by adjusting τ_1 and τ_2 for this study, in which 0.5 M phosphate buffer (KH_2PO_4–K_2HPO_4 = 9:1) was used as a solvent. It can be seen that increasing τ_1 but keeping τ_2 constant caused G_{SS_2} to decrease but caused s_2/s_1 to increase. On the other hand, keeping τ_1 constant but increasing τ_2 caused both G_{SS_2} and s_2/s_1 to decrease. It was found that only one pair of τ_1 and τ_2 simultaneously provided good agreement of both experimental G_{SS_2} and s_2/s_1 with the calculated values of G_{SS_2} and s_2/s_1. For example, a pair of values τ_1 = 6.00 and τ_2 = 10.0 showed that both calculated values of G_{SS_2} and s_2/s_1 were higher than experimental values. If τ_2 was increased to 18.0, it is seen from Table I that calculated G_{SS_2} was too high but s_2/s_1 was too low. Minimizing the deviation of calculated values from experimental values indicated that τ_2 = 26.0 was the best choice for τ_1 = 6.00. Similarly, at τ_1 = 6.50, τ_2 = 18.0 was best. Note that the best fit at τ_1 = 6.00 yielded a calculated G_{SS_2} that was too high and a calculated s_2/s_1 that was too low; but the best fit at τ_1 = 6.50 yielded opposite results, as the calculated G_{SS_2} value was too low and s_2/s_1 was too high. On the other hand, the best fit for τ_1 fixed at 6.25 yielded a τ_2 = 22.0 and gave good agreement between calculated and experimental values. The computer program that utilized a smaller $\Delta\tau_1$ and $\Delta\tau_2$ increment showed that a value of τ_1 = 6.30 and of τ_2 = 21.0 provided calculated values of G_{SS_2} as 1.33×10^{-11} and s_2/s_1 as 1.31, which are in exact agreement with the experimentally obtained values.

Table II tabulates the combinations of τ_1 and τ_2 that gave the best simultaneous fits for the theoretical and experimental values of G_{SS_2} and s_2/s_1 for the boundary conditions of the precipitation model using the method described in Table I. In addition, the re-

[6] IBM 360.

Table I—Results of Calculation $G_S s_2$ and s_2/s_1 by Adjusting τ_1 and τ_2 for Case I, Using $\Delta\tau_1$ Increments of 0.25 and $\Delta\tau_2$ Increments of 4.0

Estimated τ_1	Estimated τ_2	$G_S s_2 \times 10^{11}$[a] Calc.	$G_S s_2 \times 10^{11}$[a] Exp.	s_2/s_1 Calc.	s_2/s_1 Exp.
6.00	10.0	1.82	1.33	1.49	1.31
	14.0	1.65		1.35	
	18.0	1.56		1.27	
	22.0	1.50		1.22	
	26.0	1.45		1.19	
	30.0	1.42		1.16	
6.25	10.0	1.70		1.61	
	14.0	1.51		1.44	
	18.0	1.41		1.34	
	22.0	1.34		1.28	
	26.0	1.30		1.24	
	30.0	1.27		1.20	
6.50	10.0	1.58		1.77	
	14.0	1.38		1.55	
	18.0	1.28		1.43	
	22.0	1.21		1.35	
	26.0	1.16		1.30	
	30.0	1.12		1.26	

[a] Mole cm.$^{-1}$ sec.$^{-1}$.

sults for the boundary conditions of the supersaturation model are also tabulated for easy comparison.

CONCLUSIONS

The calculated results tabulated in Table II can also be used to show that the boundary conditions of the precipitation model are more appropriate for this drug matrix system; *i.e.*, precipitation of benzoic acid is occurring in Region 2. The variation of the values of τ_2 obtained from both cases differed markedly, as shown by their respective means and variances.

The standard deviation of the τ_2 values obtained using the boundary conditions of the precipitation model was much smaller than that for the boundary conditions of the supersaturation model. A test of their respective variances showed that statistically a difference of this magnitude occurs less than one time out of 1000 trials ($F = 2500$). In addition, a test of the means also showed that statistically a difference of this magnitude occurs less than one time out of 100 trials ($t = 27$). This strongly suggests that precipitation in Region 2 occurs in this matrix solvent system.

Secondly, comparison of τ_1 values shows that both cases optimized at the same values of τ_1. This was not unexpected, however, since Region 1 is identical in both models. Obtaining identical optimum values as predicted by the models was very encouraging since vastly different conditions in Region 2 were used in the theoretical equations. These values are in fair agreement with those found under more ideal conditions, *i.e.*, experiments ($\tau_1 = 5.5$) in 0.50 *N* HCl with no surfactant present. The average dioctyl sodium sulfosuccinate value of τ_1 ($\bar{\tau}_1 = 4.7$) for a 1:3 ratio was found to be in excellent agreement with that found previously (5) in hydrochloric acid solution for the same ratio ($\tau_1 = 4.5$). A test of the means indicated that these differences were insignificant. Comparison of τ_2 values shows that the two cases markedly differ. The τ_2 values obtained from the precipitation model more closely agree with the value obtained ($\tau_2 = 14.5$) under more ideal conditions, *i.e.*, experiments in 0.50 *N* HCl saturated with benzoic acid. The values of τ_2 obtained under Case II, however, are much greater than the values obtained under more ideal conditions. In addition, *a priori* consideration would dictate that values of τ_2 close to 1000 should be rejected. The above analysis strongly indicates that it should be concluded that precipitation is occurring in Region 2.

Table II also shows that the effects of surfactant can be appreciable, which indicates that wetting and variations in wetting may have contributed to some of the nonconstancy of τ_1 and τ_2 values. When surfactant was present, both the τ_1 and the τ_2 values were 10–50% smaller than in the absence of surfactant. This would be consistent with the idea that in the absence of surfactant, some of the channels (pores) for diffusion are not available and also that a lower than expected effective porosity is reflected in larger effective tortuosity values.

The results of this study clearly show that a theoretical model and mathematical analysis can be usefully employed to obtain information which cannot be obtained by ordinary methods of experimentation. It is believed that this approach can and should be extended to other situations involving such simultaneous polyphasic, polycomponent interactions.

APPENDIX

When the amounts of dissolved drugs remaining in the pores are negligible as compared to the amounts of drug released, which is true for poorly soluble drugs, the total amounts of benzoic acid and salicylic acid released, Q_B and Q_S, may be expressed by:

$$Q_B = s_1 A_{HB} \qquad \text{(Eq. A1)}$$

and:

$$Q_S = s_2 A_{HS} \qquad \text{(Eq. A2)}$$

Table II—Tabulation of Best-Fit Values of τ_1 and τ_2 and Comparison of the Calculated Parameters of $Q_S/t^{1/2}$ and s_2/s_1 with the Experimentally Observed Values for Both the Precipitation (Case I) and Supersaturation (Case II) Models

Solvent: Buffer[a] Ratio	Solvent: Total Buffer[b]	Solvent: Percent Dioctyl Sodium Sulfosuccinate	Estimated τ_1	Estimated τ_2: Case I	Estimated τ_2: Case II	$Q_S/t^{1/2} \times 10^5$[c] Calc.: Case I	$Q_S/t^{1/2} \times 10^5$[c] Calc.: Case II	$Q_S/t^{1/2} \times 10^5$[c] Exp.	s_2/s_1 Calc.: Case I	s_2/s_1 Calc.: Case II	s_2/s_1 Exp.
9:1	0.50	—	6.30	21.0	172.0	1.41	1.41	1.41	1.31	1.31	1.31
9:1	0.25	—	7.00	17.0	508.0	1.17	1.17	1.17	1.37	1.17	1.38
9:1	0.25	0.01	4.90	7.0	214.0	1.63	1.63	1.63	1.56	1.56	1.56
9:1	0.10	—	4.43	23.0	120.4	1.21	1.26	1.21	1.28	1.36	1.28
9:1	0.10	0.01	3.95	11.0	79.6	1.44	1.43	1.43	1.44	1.43	1.44
1:1	0.50	—	7.00	24.0	54.0	2.56	2.55	2.55	1.34	1.34	1.34
1:1	0.25	—	5.58	12.0	98.0	2.36	2.36	2.36	1.50	1.50	1.50
1:1	0.25	0.01	4.43	13.0	104.0	2.49	2.50	2.50	1.40	1.41	1.40
1:1	0.10	—	5.93	14.0	508.0	1.69	1.67	1.67	1.53	1.54	1.53
1:1	0.10	0.01	4.58	11.0	394.0	1.92	1.92	1.90	1.52	1.53	1.53
1:1	0.10	0.02	3.85	15.0	512.0	1.90	1.91	1.90	1.36	1.38	1.38
1:9	0.50	—	6.85	19.0	21.0	3.54	3.55	3.55	1.42	1.42	1.42
0:1	0.50	—	7.20	19.0	22.0	3.67	3.67	3.66	1.43	1.43	1.43
0:1	0.25	—	6.83	33.0	150.0	2.50	2.50	2.45	1.26	1.26	1.26
0:1	0.25	0.01	6.38	20.0	88.0	2.76	2.76	2.76	1.38	1.38	1.38
0:1	0.10	—	7.25	32.0	996	1.73	1.57	1.60	1.26	1.26	1.26
0:1	0.10	0.01	5.08	20.0	475.0	2.05	2.05	2.05	1.33	1.33	1.33

[a] KH_2PO_4–K_2HPO_4 in molar ratio. [b] Moles/l. [c] g. cm.$^{-2}$ sec.$^{-1/2}$.

Differentiation with respect to time and rearrangement of these equations yield:

$$s_1\,ds = \frac{G_B s_1}{A_{HB}}\,dt \qquad \text{(Eq. A3)}$$

and:

$$s_2\,ds = \frac{G_S s_2}{A_{HS}}\,dt \qquad \text{(Eq. A4)}$$

where:

$$G_B = \frac{dQ_B}{dt} \text{ and } G_S = \frac{dQ_S}{dt} \qquad \text{(Eq. A5)}$$

It can be assumed that $G_B s_1$ and $G_S s_2$ are constants in time. Equations A3 and A4 show that this assumption simply means that Q_B and Q_S are both proportional to the square root of time, which is a fact supported by the experimental data given in Figs. 2–5. Integration of Eq. A3 from $s = 0$ at $t = 0$ to $s = s$ at $t = t$ gave:

$$s_1 = \left(\frac{2G_B s_1 t}{A_{HB}}\right)^{1/2} \qquad \text{(Eq. A6)}$$

Substitution of Eq. A6 into Eq. A1, with subsequent rearrangement, gave Eq. 25 shown in the text:

$$G_B s_1 = \frac{1}{2A_{HB}}\left(\frac{Q_B}{t^{1/2}}\right)^2 \qquad \text{(Eq. 25)}$$

The same relationship for s_2 and $G_S s_2$ may be obtained by integrating Eq. A4 and substituting the result into Eq. A2; *i.e.*:

$$s_2 = \left(\frac{2G_S s_2 t}{A_{HS}}\right)^{1/2} \qquad \text{(Eq. A7)}$$

and:

$$G_S s_2 = \frac{1}{2A_{HS}}\left(\frac{Q_S}{t^{1/2}}\right)^2 \qquad \text{(Eq. 26)}$$

The latter equation corresponds to Eq. 26 of the text.

The ratio of the solid drug–solvent boundaries can then easily be obtained from the equations to obtain Eq. 27 of the text:

$$\frac{s_2}{s_1} = \left(\frac{G_S s_2 \cdot A_{HB}}{G_B s_1 \cdot A_{HS}}\right) \qquad \text{(Eq. 27)}$$

REFERENCES

(1) S. J. Desai, A. P. Simonelli, and W. I. Higuchi, *J. Pharm. Sci.*, **54,** 1459(1965).

(2) S. J. Desai, P. Singh, A. P. Simonelli, and W. I. Higuchi, *ibid.*, **55,** 1224(1966).

(3) *Ibid.*, **55,** 1230(1966).

(4) *Ibid.*, **55,** 1235(1966).

(5) P. Singh, S. J. Desai, A. P. Simonelli, and W. I. Higuchi, *J. Pharm. Sci.*, **56,** 1542(1967).

(6) *Ibid.*, **56,** 1548(1967).

(7) *Ibid.*, **57,** 217(1968).

(8) J. B. Schwartz, A. P. Simonelli, and W. I. Higuchi, *J. Pharm. Sci.*, **57,** 274(1968).

(9) *Ibid.*, **57,** 278(1968).

(10) S. J. Desai, Ph.D. thesis, University of Michigan, Ann Arbor, Mich., 1966.

(11) J. B. Schwartz, Ph.D. thesis, University of Michigan, Ann Arbor, Mich., 1967.

(12) P. Singh, Ph.D. thesis, University of Michigan, Ann Arbor, Mich., 1967.

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